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Date of mailing (day/month/year) 21 April 1999 (21.04.99)	
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International filing date (day/month/year) 07 August 1998 (07.08.98)	Priority date (day/month/year) 15 August 1997 (15.08.97)
Applicant SHERMAN, Bernard, Charles	

1. The designated Office is hereby notified of its election made:

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/545, 9/14, 9/20	A1	(11) International Publication Number: WO 99/08683 (43) International Publication Date: 25 February 1999 (25.02.99)
(21) International Application Number: PCT/CA98/00773 (22) International Filing Date: 7 August 1998 (07.08.98) (30) Priority Data: 2,209,868 15 August 1997 (15.08.97) CA (71)(72) Applicant and Inventor: SHERMAN, Bernard, Charles [CA/CA]; 50 Old Colony Road, Willowdale, Ontario M2L 2K1 (CA).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: PHARMACEUTICAL COMPOSITIONS COMPRISING CEFUROXIME AXETIL (57) Abstract A co-precipitate of cefuroxime axetil and a water-soluble excipient. Process for making said co-precipitate, and pharmaceutical compositions for oral administration comprising said co-precipitate.		

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**PHARMACEUTICAL COMPOSITIONS COMPRISING
CEFUROXIME AXETIL**

BACKGROUND

5 Cefuroxime axetil is an antibiotic effective against a wide spectrum of microorganisms. Antibiotics for oral administration should be in a form which provides high bioavailability, whereby absorption into the bloodstream from the gastro-intestinal tract is maximized.

10 For cefuroxime axetil, the prior art discloses substantial difficulties in making compositions for oral administration providing high bioavailability.

Pure cefuroxime axetil can be produced in crystalline form or amorphous form. U.S. patent 4820833 discloses that the pure amorphous form is more soluble in
15 water than the pure crystalline form and gives higher bioavailability upon oral administration.

U.S. patent 4897270 further discloses that film coated tablets comprising cefuroxime axetil (even in amorphous form) give low levels of absorption into the
20 blood stream unless the tablets are formulated such that, when the tablet is ingested, the film coating ruptures very rapidly and the core then disintegrates immediately.

The prior art thus teaches that good absorption from tablets comprising
25 cefuroxime axetil can be achieved only if the cefuroxime axetil used in the formulation is in pure amorphous form and the tablets contain sufficient disintegrant to cause them to disintegrate immediately in gastro-intestinal fluid.

It is the object of the present invention to overcome these limitations disclosed
30 in the prior art.

More specifically, one object of the present invention is to enable compositions of cefuroxime axetil for oral administration exhibiting high bioavailability without requiring use of cefuroxime axetil in pure amorphous form; and a second object
5 of the present invention is to enable tablets for oral administration exhibiting high bioavailability without requiring that the tablets disintegrate immediately in gastro-intestinal fluid.

BRIEF SUMMARY OF THE INVENTION

10

It has been found that the water solubility and hence bioavailability of cefuroxime axetil can be enhanced by making a co-precipitate comprising cefuroxime axetil and a water-soluble excipient.

15

It has further been found that tablets made from the co-precipitate exhibit satisfactory dissolution and bioavailability even if the tablets disintegrate over a period of many minutes, instead of immediately.

DETAILED DESCRIPTION OF THE INVENTION

20

As aforesaid, it has been found that the water-solubility of cefuroxime axetil can be enhanced by making a co-precipitate of cefuroxime axetil with a water-soluble excipient.

25

The term "water-soluble excipient" will be understood to mean an ingredient having no therapeutic activity and being nontoxic (and thus suitable as an excipient) that has a solubility in water of at least 1 g per 1000 g at 20°C. The solubility will preferably be at least 1 g per 100 g at 20°C, and more preferably at least 1 g per 10 g at 20°C. Suitable water-soluble excipients will include, for
30 example, povidone, polyethylene glycols, hydroxypropyl cellulose, methylcellulose, lactose, mannitol and sorbitol.

5 A preferred water-soluble excipient is povidone. The amount of the water-soluble excipient used may be from about 2% to about 60% of the total weight of the co-precipitate, preferably from about 5% to about 25%, and most preferably about 10%.

10 The co-precipitate is made by dissolving pure crystalline cefuroxime axetil and the water-soluble excipient in a solvent or combination of solvents and evaporating the solvent or solvents. The solvent or solvents used will preferably be a solvent or solvents in which the cefuroxime axetil and the water soluble excipient have relatively high solubility so as to minimize the amount of solvent needed.

15 Since cefuroxime axetil has low solubility in water, it follows that a solvent other than water must be used to dissolve the cefuroxime axetil. Of the common organic solvents, the solvent in which cefuroxime axetil is most soluble is acetone. Acetone is thus a preferred solvent.

20 If the solvent selected to dissolve the cefuroxime axetil is also a good solvent for the water-soluble excipient, then only this one solvent is needed to dissolve both. However, if the solvent selected to dissolve the cefuroxime axetil is not a good solvent for the selected water-soluble excipient, then a second solvent is needed to dissolve the water-soluble excipient. That second solvent may be water or another organic solvent.

25 If two solvents are used, they should be capable of being inter-dissolved to enable formation of a clear solution of the cefuroxime axetil and the water-soluble excipient in the combination of solvents.

30

5 A solution of the cefuroxime axetil and water-soluble excipient in the solvent or solvents may be prepared either by dissolving the cefuroxime axetil and water-soluble excipient into solvents separately and then mixing the two solutions together, or by directly adding the cefuroxime axetil and water-soluble excipient to the solvent or mixture of solvents and mixing until a clear solution is formed.

10 After the solution of the cefuroxime axetil and water-soluble excipient in the solvent or solvents is prepared, it is necessary to then remove the solvent or solvents to obtain a dry co-precipitate.

15 This may be done, for example, by evaporating the solvent or solvents in a spray drying or roller drying process, or by evaporating the solvent or solvents under vacuum.

The dried co-precipitate comprising cefuroxime axetil and the water-soluble excipient will then be further processed into a tablet.

20 This may be done by mixing the co-precipitate with other excipients and then processing the mixed powder into tablets on a tablet press. The other excipients will preferably include both a disintegrant and a lubricant.

25 The disintegrant is an ingredient which absorbs water and swells to cause the tablet to disintegrate when the tablet is immersed in gastro-intestinal fluid. Preferred disintegrants are water-insoluble cross-linked polymers, including, for example, croscarmellose sodium, sodium starch glycolate, and crospovidone.

30 A lubricant is needed to prevent sticking of the powder to the tooling in the tableting process. Preferred lubricants are stearic acid and metallic stearates, such as magnesium stearate.

It will be understood that, as an alternative to preparing the dry co-precipitate by evaporation of solvents and then mixing the co-precipitate with other excipients in a subsequent step, the two steps may be done together. This may be done,
5 for example, by spraying the solution of cefuroxime axetil and the water-soluble excipient onto other excipients in a fluidized bed drying system.

The invention will be further illustrated by the following examples, which are intended to be illustrative but not limiting of the scope of the invention.

10

EXAMPLE 1

2000 g of acetone and 200 g of methanol were placed in a beaker. While stirring, 500 g of pure crystalline cefuroxime axetil was slowly added, and stirring
15 was continued for about 5 minutes, until the cefuroxime axetil was fully dissolved. Stirring was continued and 50 g of hydroxy propyl cellulose was then added. Stirring was continued for another several minutes, until the hydroxy propyl cellulose was fully dissolved. The solution was then spray-dried to obtain a co-precipitate comprising 1 part hydroxypropyl cellulose to 10 parts cefuroxime
20 axetil.

EXAMPLE 2

The following were mixed together:

25

co-precipitate from example 1	-	134.2 g
croscarmellose sodium	-	44.0 g
magnesium stearate	-	1.0 g
colloidal silicon dioxide	-	<u>0.8 g</u>
30 Total	-	180.0 g
		=====

The mixed powder was compacted into slugs on a tablet press. The slugs were then ground into granules, and the granules were recompressed on a tablet press into tablets of weight 900 mg.

5

In view of the proportions of ingredients as aforesaid, each tablet contained 671 mg of co-precipitate, which in turn contained 610 mg of cefuroxime axetil, which in turn is equivalent to about 500 mg of cefuroxime.

10

The tablets were tested for disintegration time using the method set out in the United States Pharmacopoeia, 23rd edition, page 1791. The disintegration time was over 30 minutes.

15

The tablets were also tested for dissolution as set out in the United States Pharmacopoeia, 23rd edition, page 316. The result was about 65% in 20 minutes and 90% in 60 minutes.

20

The dissolution specifications for cefuroxime axetil tablets on the said page 316 are 65% in 20 minutes and 80% in 60 minutes. The tablets of this example were thus found to comply with this specification, despite the relatively slow disintegration.

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The dissolution specifications in the United States Pharmacopoeia are designed to ensure that tablets meeting the specifications will exhibit acceptable bioavailability.

EXAMPLE 3

30

2000 g of acetone and 200 g of methanol were placed in a beaker. While stirring, 500 g of pure crystalline cefuroxime axetil was slowly added, and stirring was continued for about 5 minutes, until the cefuroxime axetil was fully dissolved. Stirring was continued and 50 g of povidone was then added. Stirring

was continued for another several minutes, until the povidone was fully dissolved. The solution was then spray-dried to obtain a co-precipitate comprising 1 part povidone to 10 parts cefuroxime axetil.

5

EXAMPLE 4

The following were mixed together:

10	co-precipitate from example 3	-	132.0 g
	croscarmellose sodium	-	43.6 g
	magnesium stearate	-	1.0 g
	colloidal silicon dioxide	-	<u>0.8 g</u>
	Total	-	177.4 g
15			=====

The mixed powder was compacted into slugs on a tablet press. The slugs were then ground into granules, and the granules were recompressed on a tablet press into tablets of weight 900 mg.

20

Again, in view of the proportions of ingredients as aforesaid, each tablet contained 670 mg of co-precipitate, which in turn contained 609 mg of cefuroxime axetil, which in turn is equivalent to about 500 mg of cefuroxime.

25 The tablets were tested for disintegration time using the method set out in the United States Pharmacopoeia, 23rd edition, page 1791. The disintegration time was about 10 minutes.

30 The tablets were also tested for dissolution as set out in the United States Pharmacopoeia, 23rd edition, page 316. The result was over 80% in 20 minutes and over 90% in 60 minutes.

The tablets of this example thus exhibited dissolution substantially faster than required by the United States Pharmacopoeia, again despite the fact that disintegration was not immediate.

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What is claimed is:

- 5 1. A co-precipitate comprising cefuroxime axetil and a water-soluble excipient.
2. A co-precipitate as in claim 1 comprising from about 40% to about 98% by weight cefuroxime axetil and from about 2% to about 60% by weight water- soluble excipient.
- 10 3. A co-precipitate as in claim 1 comprising from about 75% to about 95% by weight cefuroxime axetil and from about 5% to about 25% by weight water-soluble excipient.
- 15 4. A co-precipitate as in claim 1 comprising about 90% by weight cefuroxime axetil and about 10% by weight water-soluble excipient.
- 20 5. A co-precipitate as in any of claims 1 to 4 wherein the water-soluble excipient is selected from the group consisting of povidone, hydroxy propyl cellulose, methycellulose, lactose, mannitol and sorbitol.
6. A process of production of a co-precipitate of any of claims 1 to 5 which comprises:-
 - 25 - dissolving the cefuroxime axetil and water-soluble excipient in a solvent or a mixture of solvents; and
 - evaporating the solvent or solvents.
7. A process as in claim 6 wherein acetone is used as solvent.
- 30 8. A process as in claim 6 wherein the solvent or solvents are evaporated by spray-drying.

9. A pharmaceutical tablet comprising a co-precipitate according to any of claims 1 to 5.
- 5 10. A pharmaceutical tablet as in claim 9 further comprising a disintegrant.
11. A pharmaceutical tablet as in claim 10 wherein the disintegrant is a water-insoluble cross-linked polymer.
- 10 12. A pharmaceutical tablet as in claim 10 wherein the disintegrant is selected from the group consisting of croscarmellose sodium, sodium starch glycolate and crospovidone.
13. A pharmaceutical tablet as in claim 10 further comprising a lubricant.
- 15 14. A pharmaceutical tablet as in claim 13 wherein the lubricant is stearic acid or a metallic stearate.

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INTERNATIONAL SEARCH REPORT

Inter national Application No
PCT/CA 98/00773

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/545 A61K9/14 A61K9/20

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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 757 991 A (ACS DOBFAR S.P.A., MILAN (IT)) 12 February 1997 see the whole document ---	1-14
A	FR 2 549 837 A (GLAXO) 1 February 1985 see the whole document ---	1-14
A	EP 0 107 276 A (GLAXO) 2 May 1984 cited in the application see claims see page 23, line 1 - line 32 ---	1-14
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern: Application No

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

19 November 1998

Date of mailing of the international search report

25/11/1998

Name and mailing address of the ISA

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Fax: (+31-70) 340-3016

Authorized officer

Scarponi, U

INTERNATIONAL SEARCH REPORT

Inter national Application No

PCT/CA 98/00773

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 280 571 A (ELI LILLY AND CO., U.S.A.) 31 August 1988 see page 3, line 1 see claims 1,5 see examples ---	1-14
A,P	WO 98 22091 A (YISSUM RES. DEV. CO., IL) 28 May 1998 see claims 1,3,9-11,13,14,16-21 ---	1-14
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PATENT COOPERATION TREATY

PCT

REC'D 31 MAY 1999

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PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PCT-1034	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/CA98/00773	International filing date (day/month/year) 07/08/1998	Priority date (day/month/year) 15/08/1997
International Patent Classification (IPC) or national classification and IPC A61K31/545		
Applicant SHERMAN, Bernard, Charles		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 4 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 10/03/1999	Date of completion of this report 27.05.99
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. (+49-89) 2399-0 Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Authorized officer Giacobbe, S Telephone No. (+49-89) 2399 

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/CA98/00773

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-8 as originally filed

Claims, No.:

1-14 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-14
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-14
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-14
	No:	Claims	

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/CA98/00773

2. Citations and explanations

see separate sheet

1. Section V

1.1 Cited Documents

The following documents (D) are referred to in this communication:

- D1: EP-A-0 757 991 (ACS DOBFAR S.P.A., MILAN (IT)) 12 February 1997
- D2: FR-A-2 549 837 (GLAXO) 1 February 1985
- D3: EP-A-0 107 276 (GLAXO) 2 May 1984 cited in the application
- D4: GB-A-2 181 052 (GLAXO) 15 April 1987 cited in the application
- D5: GB-A-2 204 792 (GLAXO) 23 November 1988
- D6: EP-A-0 280 571 (ELI LILLY AND CO., U.S.A.) 31 August 1988
- D7: WO 98 22091 A (YISSUM RES. DEV. CO., IL) 28 May 1998
- D8: EP-A-0 821 965 (BASF) 4 February 1998

1.2 Art 33(2) PCT (Novelty)

The present application meets the requirements of Article 33(2) PCT, because the subject-matter of claims 1-14 is new.

The subject-matter of independent claim is new because the previous art documents D1-D8 do not disclose any co-precipitate of cefuroxime axetil and a water-soluble excipient. The co-precipitate being new, also the process for making it and compositions containing it are new.

1.3 Art 33(3) PCT (Inventive step)

The present application does meet the requirements of Article 33(3) PCT, because the subject-matter of claims 1-14 does involve an inventive step.

The technical problem which the present application sought to solve vis-à-vis any of the prior art documents D1-D8 is *"how to find an alternative bioavailable formulation of cefuroxime axetil"*. The solution proposed, i.e. the co-precipitation of cefuroxime axetil with a water-soluble excipient, cannot be derived from such documents by the person skilled in the art without the exercise of inventive abilities and therefore it involves an inventive step.

09/485558

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference PCT-1034	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/CA 98/ 00773	International filing date (day/month/year) 07/08/1998	(Earliest) Priority Date (day/month/year) 15/08/1997
Applicant SHERMAN, Bernard, Charles		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. ☐ Certain claims were found unsearchable (see Box I).
2. ☐ Unity of invention is lacking (see Box II).
3. ☐ The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing
 - ☐ filed with the international application.
 - ☐ furnished by the applicant separately from the international application,
 - ☐ but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
 - ☐ Transcribed by this Authority
4. With regard to the **title**, ☒ the text is approved as submitted by the applicant
 - ☐ the text has been established by this Authority to read as follows:
5. With regard to the **abstract**, ☒ the text is approved as submitted by the applicant
 - ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.
6. The figure of the **drawings** to be published with the abstract is:
 - Figure No. ☐ as suggested by the applicant. ☐ None of the figures.
 - ☐ because the applicant failed to suggest a figure.
 - ☐ because this figure better characterizes the invention.

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/CA 98/00773

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/545 A61K9/14 A61K9/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 757 991 A (ACS DOBFAR S.P.A., MILAN (IT)) 12 February 1997 see the whole document ---	1-14
A	FR 2 549 837 A (GLAXO) 1 February 1985 see the whole document ---	1-14
A	EP 0 107 276 A (GLAXO) 2 May 1984 cited in the application see claims see page 23, line 1 - line 32 ---	1-14
A	GB 2 181 052 A (GLAXO) 15 April 1987 cited in the application see the whole document ---	1-14
A	GB 2 204 792 A (GLAXO) 23 November 1988 see the whole document ---	1-14
-/--		



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"Z" document member of the same patent family

Date of the actual completion of the international search

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Name and mailing address of the ISA

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INTERNATIONAL SEARCH REPORT

International Application No.

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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